REMARKS

Upon entry of the present amendments, claims 52-65 and 67-75 are pending in the application. Claim 66 has been cancelled herein without prejudice or disclaimer. Claims 61-62, 71-74, and 75 have been amended herein to more particularly define the subject matter of the invention. Support for these amendments can be found throughout the specification. Thus, no new matter has been added.

Applicants acknowledge with appreciation that the rejection of claims 1-2, 5, 7-10, 13, 16, 20 and 25 under 35 U.S.C. § 101; the rejection of claims 3, 4, 6, 11-12, 14-15, 17-19, 22, 24, and 26 under the judicially created doctrine of obviousness-type double patenting; and the rejection of claims 1-20, 22, and 24-26 under 35 U.S.C. § 112, second paragraph have been withdrawn.

Applicants also note with appreciation that the Examiner has indicated that claims 52-60 and 63-64 have been allowed.

In addition, Applicants note that the Examiner indicated on the Office Action Summary page that claim 65 has been rejected. However, this claim is not specifically rejected in the instant Office Action. Accordingly, Applicants respectfully request clarification of the status of this claim.

Information Disclosure Statement

The Examiner has noted that, despite the Applicants' statement to the contrary, no new IDS was submitted along with the Amendment and Response filed on September 7, 2004. Applicants thank the Examiner for pointing out this discrepancy. In connection with the Request for Continued Examination being submitted herewith, Applicants also submit a copy of the Information Disclosure Statement referred to at page 8 of the Amendment and Response filed on September 7, 2004.

Claim Rejections -- 35 U.S.C. § 112, first paragraph

Claims 66-72 have been rejected under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for a method for producing a population of highly enriched human CNS stem cells using identifiable/deposited antibodies, does not reasonably provide

enablement for methods of isolating highly enriched populations of human CNS stem cells using unknown or uncharacterized antibodies, or using unknown and undescribed 'selecting' methodology." (Office Action at page 3).

Specifically, the Examiner indicates that the specification indicates that only embryonic CNS brain regions and certain regions within the adult CNS (such as the subventricular regions and the dentate gyrus of the hippocampus) contain CNS neural stem cells. Thus, the Examiner concludes that claims 66-70 do not reasonably contain neural stem cells after-the-fact, and therefore are not commensurate in scope with the guidance provided by the instant specification or that accepted within the state of the art at the time of filing of the Applicants' invention, as illustrated by the teachings of the Weiss patent. (*See* Office Action at pages 3-4). The Examiner's rejection appears to be based on the Examiner's position that in the juvenile/adult, neural stem cells may only be derived from the subventricular regions or the dentate gyrus of the hippocampus. Applicants disagree.

The instant specification incorporates two United States Patents by reference (US Patent Nos. 5,851,832 and 5,750,376 ("the Weiss patents")). These patents provide ample guidance as to how neural stem cells can be obtained from both embryonic and adult tissues.

First, the Weiss patents teach that the claimed neurospheres/neural stem cell compositions can be obtained from embryonic, fetal, post-natal, juvenile or adult neural tissue:

> "Multipotent neural stem cells can be obtained from **embryonic, post-natal, juvenile or adult neural tissue**. ... Human heterologous neural stem cells may be derived from **fetal tissue following elective abortion, or from a post-natal, juvenile or adult organ donor**." US Patent No. 5,851,832 at col. 13, lines 14-16 and 45-47.

Second, the specification also teaches that the claimed neurospheres/neural stem cell compositions can be obtained from many regions in the brain, not merely the subependymal regions or the dentate gyrus:

> "In the case of a heterologous donor animal, the animal may be euthanized neural tissue and specific area of interest removed using a sterile procedure. Areas of particular interest include any area from which neural stem cells can be obtained that will serve to restore function to a degenerated area of a host's nervous system, particularly the host's CNS. Suitable areas include the **cerebral cortex,**

> **cerebellum, midbrain, brainstem, spinal cord and ventricular tissue**, and areas of the PNS including the carotid body and the adrenal medulla. Preferred areas include **regions in the basal ganglia, preferably the striatum which consists of the caudate and the putamen**, or various cell groups such as **the globus pallidus, the subthalamic nucleus, the nucleus basalis** which is found to be degenerated in Alzheimer's Disease patients, or the substantia nigra pars compacta which is found to be degenerated in Parkinson's Disease patients." US Patent No. 5,851,832 at col. 13, lines 21-36.
>
> "**Particularly preferred neural tissue is obtained from ventricular tissue that is found lining CNS ventricles and includes the subependyma**. The term 'ventricle' refers to any cavity or passageway within the CNS through which cerebral spinal fluid flows. Thus, the term encompasses not only the lateral, third, and fourth ventricles but also encompasses the central canal, cerebral aqueduct, and other CNS cavities." US Patent No. 5,581,832 at col. 13, lines 37-44.
>
> "Autologous neural tissue can be obtained by biopsy, or from patients undergoing neurosurgery in which **neural tissue is removed, for example, during epilepsy surgery, temporal lobectomies and hippocampalectomies.**" US Patent No. 5,851,832 at col. 13, lines 47-51.
>
> "**Neural stem cells have been isolated from a variety of adult ventricular regions, including frontal lobe, conus medullaris, thoracic spinal cord, brain stem, and hypothalamus**, and proliferated in vitro using the methods detailed herein." US Patent No. 5,851,832 at col. 13, lines 51.55.

Third, both intrinsic evidence and extrinsic evidence (detailed below) demonstrate that the claimed neurosphere/neural stem cell cultures can be obtained from a variety of regions in the juvenile/adult mammalian CNS, including regions other than the subependymal regions, precisely as stated in the specification.

Specifically, the Weiss patents provide numerous working examples that demonstrate the generation of the claimed neurospheres/neural stem cell compositions from embryonic/fetal mouse and human neural tissue (*See* Examples 1, 3, 4, and 9), as well as from various juvenile and adult rodent, primate and human neural tissues, including: (1) **striatum including subependymal region** (*See* Ex. 2 and 5 -- juvenile and adult mouse); (2) **frontal lobe** (*See* col. 13, line 53; see also Example 11 -- adult human, the right frontal lobe from the tip of the frontal/anterior horn of the lateral ventricle); (3) **conus medullaris** (*See* col. 13, line 53; see also Example 10 -- adult primate conus medullaris); (4) **thoracic spinal cord** (See col. 13, line 54); (5) **brain stem** (*See* col. 13, lines 53-54); (6) **hypothalamus** (*See* col. 13, line 54). *See also, e.g.*, Represa et al., Eur. J. Neuroscience, 14, pp. 452-462 (2001) (confirming that the claimed neurosphere/neural stem cell cultures can be obtained from **spinal cord,** as described in the

specification) (courtesy copy enclosed).

In addition, there are multiple reports from peer-reviewed publications, which confirm that the claimed neurosphere/neural stem cell cultures can be obtained from various regions of adult mammalian CNS, including cerebral cortex, amygdala and hippocampus, precisely as stated in the specification, using the methods described in the specification:

amygdala (part of the cerebral cortex)

Arsenijevic et al., "Isolation of Multipotent Neural Precursors Residing on the Cortex of the Adult Human Brain", Exp. Neurology, 170, pp. 48 - 62 (2001) (confirming that the claimed human neurosphere/neural stem cell cultures can be obtained from amygdala by biopsy using the methods described in the specification -- see p. 53 right column) (courtesy copy enclosed).

temporal cortex and frontal cortex (part of the cerebral cortex)

Arsenijevic et al., "Isolation of Multipotent Neural Precursors Residing on the Cortex of the Adult Human Brain", Exp. Neurology, 170, pp. 48 - 62 (2001) (demonstrating that the claimed human neurosphere/neural stem cell cultures can be obtained from temporal cortex and frontal cortex by lobectomy using the methods described in the specification -- see p. 53 right column).

hippocampus

Johansson et al., "Neural stem cells in the adult human brain", Exp. Cell Res., 253, pp. 733-36 (1999) (confirming that the claimed human neural stem cell cultures can be obtained from hippocampus using the methods described in the specification) (courtesy copy enclosed);

Toda et al., "Neurons generated from adult rat hippocampal cells form functional glutamatergic and GABAergic synapses in vitro", Exp. Neurol., 165, pp. 66-76 (2000) (confirming that the claimed neural stem cell cultures can be obtained from rat hippocampus using the methods described in the specification) (courtesy copy enclosed);

Arsenijevic et al., "Isolation of Multipotent Neural Precursors Residing on the Cortex of the Adult Human Brain", Exp. Neurology, 170, pp. 48 - 62 (2001) (confirming that the claimed human neurosphere/neural stem cell cultures can be obtained from hippocampus by hippocampalectomy using the methods described in the specification -- see p. 53 right column).

In sum, the instant specification, the disclosure of the Weiss patents as well as voluminous confirmatory extrinsic evidence, demonstrate that the claimed neurosphere/neural stem cell cultures can be obtained (using the methods described in the specification and the Weiss patents) from numerous of the adult brain regions -- namely the cerebral cortex, brainstem, spinal cord, temporal lobe, hippocampus and ventricular regions including the subependymal region.

Fourth, the case law is clear that the enablement requirement is met if the description

enables **any** mode of making and using the claimed invention. See Engel Industries Inc. v. Lockformer Company, 946 F.2d 1528, 1533 (Fed. Cir. 1991); Johns Hopkins University v. CellPro, Inc., 152 F.3d 1342, 1361 (Fed. Cir. 1998). Here, there is no dispute that Applicants have provided not just one mammalian CNS source for obtaining the claimed neurosphere/neural stem cell cultures, but have provided numerous sources, including embryonic/fetal CNS, as well as multiple regions from the juvenile and adult mammalian CNS.

In addition, the law states that where, as here, the specification contains a teaching of the process of making the claimed invention, the specification must be taken as in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the statements in the specification. See In re Marzocchi, 439 F.2d 220, 224 (CCPA 1971). Here there is no reason to doubt the objective truth of the statements in the specification or in the Weiss patents, which expressly state that the claimed cultures can be obtained from embryonic/fetal CNS and from juvenile/adult mammalian CNS, including cerebral cortex, brainstem, spinal cord and ventricular tissue (*See* Weiss patents col. 13, lines 27-29). Moreover, the extrinsic evidence presented herein also confirms the objective truth of these statements. The claimed neurosphere/neural stem cell cultures can be obtained from a wide variety of tissues in the embryonic/fetal and the juvenile/adult mammalian CNS. For this reason too, the claims are enabled.

Thus, Applicants contend that, contrary to the Examiner's contention, the multipotent neural stem cells can be obtained from a wide range of embryonic and adult neural tissues. Therefore, Applicants submit that one skilled in the art would be able to make and use the invention recited in claims 67-70 without undue experimentation. Thus, this rejection of the claims should be withdrawn.

Moreover, with respect to claims 71 and 72, the Examiner has indicated that, because these claims do not set forth any "structural characterization and little functional characteristics for determining when the skilled artisan is in possession of the required components necessary for pacticing the instant invention, and in contrast, still encompass use of any biologically functional equivalent antibody, or use of other unknown 'selecting' procedures/reagents not described within the instant specification. Therefore, the lack of guidance provided in the specification as to what minimal structural components are necessarily for practicing the

currently claimed invention . . . would prevent the skilled artisan from knowing how to make and use the instant invention without requiring undue experimentation to determine otherwise . . ." (Office Action at page 4).

As amended herein, claims 71 and 72 now recite specific antibody designations. Specifically, amended claim 71 specifies that the method for producing a population enriched for human CNS-SC which can initiate neurospheres (NS-IC) can be obtained by selecting from a population of neural or neural-derived cells for cells that bind to monoclonal antibody AC133 or to monoclonal antibody 5E12 or to both and by selecting and eliminating from the population those cells that are $CD45^+$, $CD34^+$, or $CD45^+CD34^+$. Likewise, claim 72 now specifies that the population of cells obtained according to the methods of claim 71 can be further enriched by selecting an eliminating those cells that bind to monoclonal antibody 8G1.

Thus, Applicants contend that the skilled artisan, with the specification in hand, would be able to practice the methods of the invention recited in claims 71 and 72, as amended herein, without undue experimentation. Therefore, amended claims 71 and 72 are fully enabled by the as-filed specification. As such, Applicants request that this rejection be withdrawn.

Claim Rejections -- 35 U.S.C. § 112, second paragraph

Claim 72 has been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. According to the Examiner, "[a]s previously made of record, in that 8G1 still appears to be antibody designation, versus a well-known antigen designation (i.e., CD24, instead; see page 9 of the specification), this claim is indefinite." (Office Action at page 5). Claim 72 has been amended herein to recite "those cell that bind to monoclonal antibody 8G1" rather than "those cells that are $8G1^+$". Thus, Applicants contend that claim 72, as amended herein, is definite, because it refers to an identifiable/deposited antibody. Therefore, this rejection should be withdrawn.

Claims 61-62 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite. According to the Examiner, "[n]o proper antecedent basis exists for '**said** antibod**ies**', versus 'monoclonal antibody' in base claims 52, 57, 58, 59, or 69." (Office Action at page 6). As

suggested by the Examiner, claims 61 and 62 have been amended herein to recite "wherein said antibodies are". Accordingly, Applicants believe that this rejection should be withdrawn.

Claim 75 has been rejected under 35 U.S.C. § 112, second paragraph, as indefinite. According to the Examiner, "[i]t remains unknown what the metes and bounds "**a** neural survival factor (NSF)" entail, when the claim is not reasonably directed to only that alternatively described on page 19 of the specification, where only the one specific NSF molecule available from Clonetics is described versus generic neural survival factors, as encompassed by the current claim language." (Office Action at page 6). As suggested by the Examiner, claim 75 has been amended to include the phrase, "comprises neural survival factor, NSF." Thus, Applicants believe that this rejection should be withdrawn.

Claims 73-75 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite. According to the Examiner, "[s]teps (e) and (f) in claim 73 are inconsistent with steps (b) and (d), in that steps (e) and (f) recite '**or** CD45- or CD34-', in which the cells must be both AC133+ 'and/or' 5E12+ '**and**' CD45- 'and/or' CD34-; thereby, making the current claims ambiguous and indefinite." (Office Action at page 6).

Applicants thank the Examiner for pointing out this discrepancy in claim 73. Claim 73 has been amended herein to make the claim more clear. Specifically, in step b), amended claim 73 now specifies that those cells that bind to monoclonal antibody AC133 or to monoclonal antibody 5E12 or to both are selected, and step d) specifies that the $CD45^+$, $CD34^+$, or $CD45^+CD34^+$ cells are then selected and removed from the population, such that the remaining cells in step d) are further enriched in the population of NS-ICs as compared with the enriched fraction obtained in step b). Finally, claim 73 specifies that at least one cell from the enriched fraction obtained in step d) is introduced into a culture medium and allowed to proliferate. Applicants submit that, as amended herein, claim 73 is neither ambiguous nor indefinite. Therefore, this rejection should be withdrawn.

Moreover, Applicants note that claims 74-75 each depend from claim 73. As such, they necessarily contain all of the limitations recited in amended claim 73. Therefore, for the reasons articulate above, Applicants contend that these claims are also neither ambiguous nor indefinite.

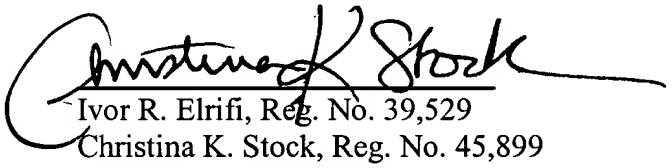
Thus, Applicants submit that this rejection of claims 73-75 should be withdrawn.

CONCLUSION

Applicants submit that this paper is fully responsive and that the application is in condition for allowance. Such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

No additional fees are believed due in connection with this paper. However, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to Deposit Account No. 50-0311, Reference 17810-510 NATL (SCI-10 NATL).

Respectfully submitted,



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